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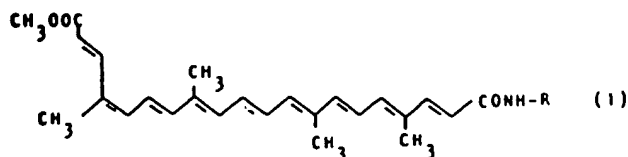
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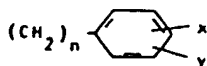
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(54) New derivatives of the 9-cis-6,6'-diapo-psi,psi-carotenedioic acid, preparation thereof and pharmaceutical compositions containing same.

(57) The invention provides new derivatives of the 9-cis-6,
 6'-diapo-psi-carotenedioic acid of general formula



wherein R is a radical selected from the group comprising



(wherein n=0,1,2 and x, y, the same or different are H,
 halogen, alkoxy, hydroxy, alkyl or trifluoromethyl radi-
 cal); 2,3-pyridyl; 4-pyridyl;
 2,3-pyridyl-methyl; 3-pyridyl-methyl.

The compounds of the formula (I) can be prepared from
 the corresponding acid by directly reacting an amine of the
 formula R-NH₂ (wherein R has the previously specified

meanings) in an aprotic solvent in the presence of an activator for the carboxylic group, or by previously transforming the above mentioned acid into the corresponding acid chloride or into the corresponding mixed anhydride and then carrying out the reaction with the amine $R-NH_2$. The compounds of formula (I) are used in pharmaceutical compositions useful in the therapeutic prevention of diseases.

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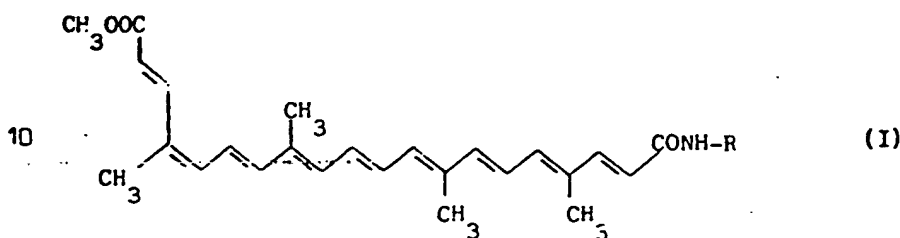
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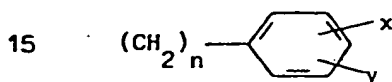
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The present invention provides to new derivatives of the 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, their preparation and the pharmaceutical compositions containing them.

5 More particularly, the present invention provides new derivatives the 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid of the general formula (I)



wherein R is a radical selected from the group comprising



(wherein $n=0,1,2$ and x,y , the same or different, are H, halogen, alkoxy, hydroxy, alkyl or trifluoromethyl radical);

2,3-pyridyl; 4-pyridyl;

20 2,3-pyridyl-methyl; 3-pyridyl-methyl.

More specifically, the present invention provides the following compounds comprised in the general formula (I)

- 1) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, benzylamide monomethyl ester;
- 25 2) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 3,4-dimethoxy-benzylamide monomethyl ester;
- 3) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, phenethylamide monomethylester;
- 4) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 3,4-dimethoxyphenethylamide monomethyl ester;
- 30

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- 5) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, anilide monomethylester;
- 6) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, p-methoxyanilide monomethylester;
- 7) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, p-chloroanilide monomethylester;
- 8) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 3,4-dichloroanilide monomethylester;
- 9) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 2,5-dimethoxyanilide monomethylester;
- 10) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 2,3-dimethylanilide monomethylester;
- 11) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, p-hydroxyanilide monomethylester;
- 12) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, m-hydroxyanilide monomethylester;
- 13) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, o-hydroxyanilide monomethylester;
- 14) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, m-fluoroanilide monomethylester;
- 15) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, p-fluoroanilide monomethylester;
- 16) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, o-fluoroanilide monomethylester;
- 17) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 4-pyridylamide monomethylester;
- 18) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 3-pyridylmethanamide monomethylester;
- 19) 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 3-trifluoromethylanilide monomethylester.

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The new products of this invention are endowed with antiproliferating activity.

As far as this activity is concerned, compound 18, tested "in vivo", has proved particularly useful.

By carrying out the test as indicated hereinbelow, the average survival time has been evaluated for mice (strain CD₂F₁) treated, or not, with compound 18.

Lymphocytic leukaemia was induced in the mice to be tested (i.p. inoculum; number of injected cells 10^6 ; tissue: ascitic fluid).

Three groups each consisting of 6 female mice have been treated. The compound has been injected using as vehicle a physiological solution with TWEEN-80 at dosages of 200, 100 and 50 mg/kg respectively.

The drug has been injected once a day for 9 days from the day immediately after the inoculum.

The used controls were 32.

The mortality of both treated mice and controls calculated on the treatment days is summarized in the following table:

Days	N° of dead animals after treatment with			N° of dead controls
	200 mg/kg	100 mg/kg	50 mg/kg	
VI				
VII				
VIII	1			8
IX				15
X				5
XI			3	4
XII	3	4	3	
XIII	2	2		
XIV				

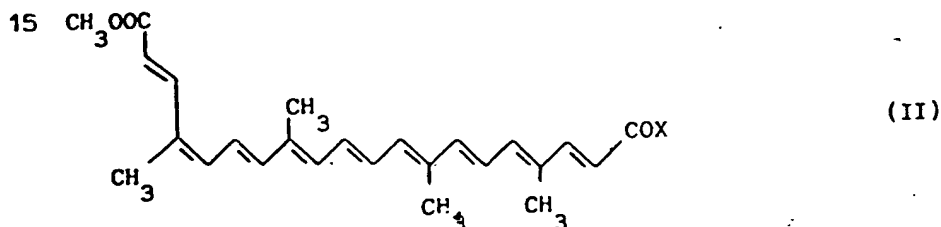
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Therefore, the average survival times are as follows:

Dosage	survival time (days)
200 mg	12.3
100 mg	12.4
50 mg	11.7
control	9.1

10. The percentage ratio (T/C) between the average survival time of the treated animals and that one of the controls is 135, 136, 128% respectively for dosages of 200, 100 and 50 mg/kg respectively.

The new compounds of the present invention can be prepared by reacting the compound of formula (II)



20 wherein X is -OH, Cl or the group O-CO-O-R₁, R₁ being CH₃, C₂H₅, C₄H₇ or CH₂CCl₃, is reacted with a compound R-NH₂ (wherein R has the previously specified meanings).

When X is -OH the reaction may be carried out in an aprotic polar solvent selected from CHCl₃, CH₂Cl₂, tetrahydrofuran and dimethyl-
25 sulfoxide, in the presence of an activator for the carboxylic group, such as for instance bicyclohexylcarbodiimide, at a temperature comprised between -10 °C and +50 °C.

When X is Cl, the acid chloride may be prepared by reacting the compound wherein X=OH with PCl₃ in a chlorinated solvent selected
30 from CHCl₃, CH₂-Cl₂ and Cl₂-CH-CH-Cl₂ and then allowing the thus

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formed acid chloride to react in situ with $R-NH_2$ in excess.

When X is $O-C-O-R_1$ the acid may be reacted in the presence of an aprotic solvent selected from CH_2Cl_2 , dioxane, tetrahydrofurane, diglyme, dimethylsulfoxide, dimethylformamide, first with an organic base selected from triethylamine, diisopropylethylamine and dimethylaniline and thereafter with a derivative of the chlorocarbonic acid of the general formula $Cl-CO-OR_1$ (wherein R_1 has the above specified meaning), at temperatures comprised between $-10^\circ C$ and $0^\circ C$.

The thus obtained mixed anhydride may be then allowed to react, in the same solvent where it has been formed, with 2 molar eq. of the amine $R-NH_2$, at temperatures comprised between $10^\circ C$ and $80^\circ C$ to yield the desired compounds.

The new compounds of the present invention are crystalline substances endowed with well defined physico-chemical characteristics and colour generally varying from orange to dark red.

For the application in the pharmaceutical field, the compounds of the invention can be made up in a suitable form for topic and systemic use (oral and injectable administration, suppositories).

To this purpose the compounds of the invention can be formulated as compositions containing, besides the active substance, the generally used solvents, excipients, adjuvants, stabilizers and vehicles.

The dosages of active substance are comprised between 1 and 500 mg.

The following examples are given to illustrate the invention without limiting it in any way.

Example 1

500 mg of monomethylester of the 9-cis-6,6'-diapo- ψ -carotene-

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dioic acid and 136 mg of benzylamine are suspended in 10 ml of CH_2Cl_2 and added with 265 mg of bicyclohexylcarbodiimide.

The thus obtained solution is left to stand for 15 h at room temperature and thereafter it is diluted with 40 ml CH_2Cl_2 . The bicyclohexylcarboureia is filtered off and then the solution is washed with diluted HCl and water, dried on Na_2SO_4 and evaporated to dryness. The residue is analysed by chromatography on silica gel using as eluent CH_2Cl_2 containing 0.5% methanol.

- 10 By crystallization from acetone, 300 mg of 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, benzylamide monomethylester (compound 1) are obtained.

m.p. = 173-175 °C; M^+ 469.

The analysis for $\text{C}_{31}\text{H}_{35}\text{NO}_3$ gives the following results:

	C	H	N
15 calculated (%)	79.28	7.51	2.98
found (%)	78.53	7.47	2.86

$\lambda_{\text{max}}^{\text{MeOH}}$ 494 m μ , 464 m μ

- 20 By working as above described, there are prepared the following compounds:

- compound 2

9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 3,4-dimethoxy-benzylamide monomethylester.

25 m.p. = 193-195 °C (CHCl_3 /acetone) M^+ 543.

The analysis for $\text{C}_{34}\text{H}_{41}\text{NO}_5$ gives the following results:

	C	H	N
calculated (%)	75.11	7.60	2.58
found (%)	74.34	7.37	2.65

30 $\lambda_{\text{max}}^{\text{MeOH}}$ 488 m μ , 459 m μ

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- compound 3

9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, phenethylamide monomethylester.

5 m.p. = 192-194 °C (dioxane) M^+ 497

The analysis for $C_{33}H_{39}NO_3$ gives the following results:

	C	H	N
calculated (%)	79.64	7.90	7.81
found (%)	79.13	7.53	2.69

10 λ MeOH 488 m μ , 459 m μ
max

- compound 4

9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 3,4-dimethoxyphenethylamide monomethylester.

15 m.p. = 200-201 °C ($CHCl_3$ /acetone) M^+ 557

The analysis for $C_{35}H_{43}NO_5$ gives the following results:

	C	H	N
calculated (%)	75.37	7.77	2.51
found (%)	75.00	7.42	2.42

20 λ MeOH 488 m μ , 459 m μ
max

Example 2.

5 g of finely grounded 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, monomethylester are suspended in 250 ml of CH_2Cl_2 cooled to 0 °C
25 and treated with 1.17 g of PCl_3 .

After 15 h at room temperature the mixture is again cooled to 0 °C
and 4.8 g of aniline are added. After 2 h at room temperature the reaction mixture is poured into 500 g of ice containing 30 ml of concentrated HCl.

30 The organic layer is separated, washed with water, with a $NaHCO_3$

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solution and again with water to neutral reaction and finally is dried on Na_2SO_4 and concentrated to dryness.

The residue is analysed by chromatography on silica gel.

- 5 As eluent CH_2Cl_2 is first used and then CH_2Cl_2 containing 1% methanol. Using this last mixture unitary fractions are obtained which by evaporation and crystallization from acetone yield 1.6 g of 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, anilide monomethylester (compound 5).

10 m.p. 173-175 °C; M^+ 469.

The analysis for $\text{C}_{31}\text{H}_{35}\text{NO}_3$ gives the following results:

	C	H	N
calculated (%)	79.28	7.51	2.98
found (%)	78.33	7.37	2.86

15 MeOH λ max 494 m μ , 464 m μ

Example 3

5 g of 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, monomethylester are suspended in 50 ml dioxane and treated with 1.5 g triethylamine. The thus obtained solution is cooled to +5 °C and added with 1.5 g of methylchloroformate. The solution is stirred at room temperature for 1.5 h; thereafter 3.0 g of p-anisidine are added. After 24 h at room temperature the reaction is completed.

The solution is evaporated to dryness and the residue is treated with acetone/ether; the thus formed solid is filtered off, washed with ether and crystallized from acetone.

2.5 g of 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, p-methoxyanilide monomethylester (compound 6) are obtained.

m.p. = 177-179 °C, M^+ 499.

30 The analysis for $\text{C}_{32}\text{H}_{37}\text{NO}_4$ gives the following results:

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	C	H	N
calculated (%)	76.92	7.46	2.80
found (%)	75.63	7.38	2.66

5 MeOH
 λ 494 m μ , 464 m μ
 max

By analogously working there are prepared the hereinbelow described compounds.

- compound 7

10 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, p-chloroanilide mono-methylester.

m.p. = 178-180 °C (acetone); M^+ 505, 503.

The analysis for $C_{31}H_{34}ClNO_3$ gives the following results:

	C	H	N
15 calculated (%)	78.87	6.80	2.78
found (%)	72.19	6.62	2.58

MeOH
 λ 494 m μ , 464 m μ
 max

- compound 8

20 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 3,4-dichloroanilide monomethylester.

m.p. = 170-172 °C (acetone); M^+ 539, 537

The analysis for $C_{31}H_{33}Cl_2NO_3$ gives the following results:

	C	H	N
25 calculated (%)	69.14	6.18	2.60
found (%)	68.56	5.97	2.45

MeOH
 λ 487 m μ , 459 m μ
 max

- compound 9

30 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 2,5-dimethoxyanilide

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monomethylester.

m.p. = 152-155 °C (acetone); M^+ 529The analysis for $C_{33}H_{39}NO_5$ gives the following results:

5		C	H	N
	calculated (%)	74.83	7.42	2.64
	found (%)	74.11	7.76	2.69

MeOH
 λ 494 m μ , 464 m μ
 max

10 - compound 10

9-cis-6,6'-diapo- ψ -carotenedioic acid, 2,3-dimethylanilide
 monomethylester.

m.p. = 187-188 °C (acetone), M^+ 497The analysis for $C_{33}H_{39}NO_3$ gives the following results:

15		C	H	N
	calculated (%)	79.64	7.90	2.81
	found (%)	78.56	7.71	2.63

MeOH
 λ 488 m μ , 460 m μ
 max

20 - compound 11

9-cis-6,6'-diapo- ψ -carotenedioic acid, p-hydroxyanilide
 monomethylester.

m.p. = 210-211 °C (dioxane); M^+ 485The analysis for $C_{31}H_{35}NO_4$ gives the following results:

25		C	H	N
	calculated (%)	76.67	7.26	2.86
	found (%)	75.05	7.15	2.65

MeOH
 λ 494 m μ , 464 m μ
 max

30 - compound 12

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9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, m-hydroxyanilide monomethylester.

m.p. = 149-152 °C (acetone); M^+ 485

5 The analysis for $C_{31}H_{35}NO_4$ gives the following results:

	C	H	N
calculated (%)	76.67	7.26	2.88
found (%)	75.97	7.43	2.80

MeOH
 λ 490 m μ , 462 m μ
 max

10

- compound 13

9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, o-hydroxyanilide monomethylester.

m.p. = 208-210 °C (acetone); M^+ 485

15 The analysis for $C_{31}H_{35}NO_4$ gives the following results:

	C	H	N
calculated (%)	76.67	7.26	2.88
found (%)	75.68	7.66	2.86

MeOH
 λ 492 m μ , 464 m μ
 max

20

- compound 14

9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, m-fluoroanilide monomethylester.

m.p. = 171-172 °C (acetone); M^+ 487

25 The analysis for $C_{31}H_{34}FNO_3$ gives the following results:

	C	H	N
calculated (%)	76.35	7.03	2.87
found (%)	75.52	6.98	2.79

MeOH
 λ 494 m μ , 462 m μ
 max

30

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- compound 15

9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, p-fluoroanilide mono-methylester.

5 m.p. = 170-171 °C (acetone); M^+ 187

The analysis for $C_{31}H_{34}FNO_3$ gives the following results:

	C	H	N
calculated (%)	76.36	7.03	2.87
found (%)	76.25	6.91	2.56

10 λ MeOH 490 m μ , 462 m μ
max

- compound 16

9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, o-fluoroanilide mono-methylester.

15 m.p. = 182-183 °C (acetone); M^+ 187

The analysis for $C_{31}H_{34}FNO_3$ gives the following results:

	C	H	N
calculated (%)	76.36	7.03	2.87
found (%)	76.13	6.90	2.98

20 λ MeOH 494 m μ , 462 m μ
max

- compound 17

9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 4-pyridylamide mono-methylester.

25 m.p. = 192-194 °C (acetone); M^+ 470

The analysis for $C_{30}H_{34}N_2O_3$ gives the following results:

	C	H	N
calculated (%)	76.56	7.28	5.95
found (%)	75.04	7.33	5.57

30 λ MeOH 490 m μ , 468 m μ
max

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- compound 18

9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 3-pyridylmethanamide monomethylester.

5 m.p. = 197-199 °C (CHCl_3 /acetone); M^+ 484

The analysis for $\text{C}_{31}\text{H}_{36}\text{N}_2\text{O}_3$ gives the following results:

	C	H	N
calculated (%)	76.83	7.49	5.78
found (%)	76.84	7.26	5.78

10 λ MeOH 489 m μ , 460 m μ
max

- compound 19

9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid, 3-trifluoromethylanilide monomethylester.

15 m.p. = 172-175 °C (acetone); M^+ 537

The analysis for $\text{C}_{32}\text{H}_{34}\text{F}_3\text{O}_3$ gives the following results:

	C	H	N
calculated (%)	71.49	6.37	2.61
found (%)	70.80	6.21	2.45

20 λ MeOH 494 m μ , 462 m μ
max

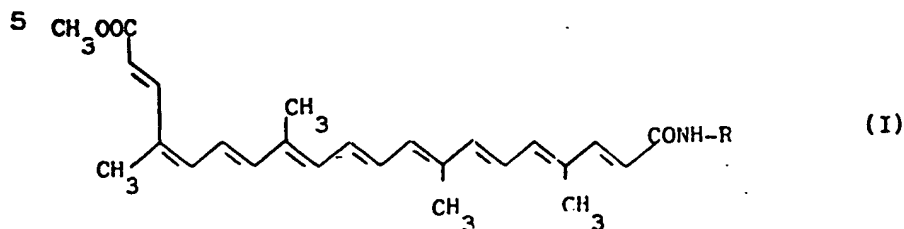
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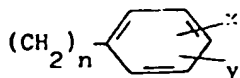
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C l a i m s:

1. Derivatives of the 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid of the general formula (I)



- 10 wherein R is a radical selected from the group comprising



(wherein $n=0,1,2$ and x,y , equal or different, are H, halogen, alkoxy, $-OH$, alkyl or trifluoromethyl radical);

2,3-pyridyl; 4-pyridyl;

2,3-pyridyl-methyl; 3-pyridyl-methyl.

2. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, benzylamide monomethylester.

- 20 3. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, 3,4-dimethoxy-benzylamide monomethylester.

4. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, phenethylamide monomethylester.

- 25 5. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, 3,4-dimethoxyphenethylamide monomethylester.

6. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, anilide monomethyl ester.

7. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, p-methoxyanilide monomethylester.

- 30 8. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, p-chloroanilide mono-

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methylester.

9. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, 3,4-dichloroanilide monomethylester.

5 10. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, 2,5-dimethoxyanilide monomethylester.

11. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, 2,3-dimethylanilide monomethylester.

12. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, p-hydroxyanilide monomethylester.

13. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, m-hydroxyanilide monomethylester.

14. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, o-hydroxyanilide monomethylester.

15 15. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, m-fluoroanilide monomethylester.

16. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, p-fluoroanilide monomethylester.

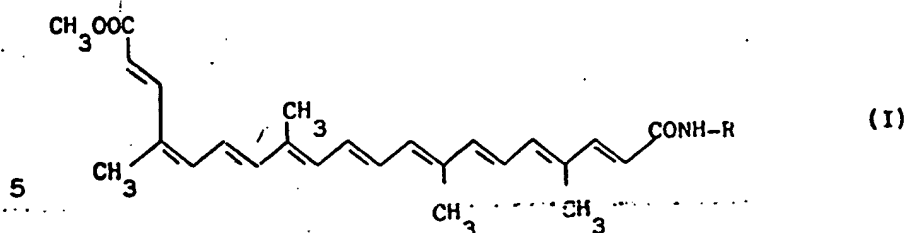
17. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, o-fluoroanilide monomethylester.

18. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, 4-pyridylmethanamide monomethylester.

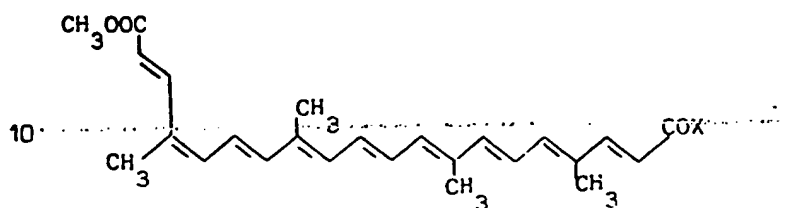
19. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, 3-pyridylmethanamide monomethylester.

25 20. 9-cis-6,6'-Diapo- $\psi\psi$ -carotenedioic acid, 3-trifluoromethylanilide monomethylester.

21. A process for the preparation of derivatives of the 9-cis-6,6'-diapo- $\psi\psi$ -carotenedioic acid of the general formula (I)



characterized in that a compound of the formula



wherein X is -OH, Cl or the group O-CO-O-R₁, R₁ being CH₃, C₂H₅, C₄H₇ or CH₂CCl₃, is reacted with a compound R-NH₂ (wherein R has
15 the above specified meanings).

22. A process according to claim 21, characterized in that when X=OH, the reaction is carried out in an aprotic solvent, in the presence of an activator for the carboxylic group, at a temperature comprised between -10 °C and +50 °C.

20 23. A process according to claim 22, characterized in that the aprotic solvent is selected from the class consisting of CHCl₃, CH₂Cl₂, tetrahydrofuran, dimethylsulfoxide.

24. A process according to claim 22, characterized in that the activator for the carboxylic group is bicyclohexylcarbodiimide.

25 25. A process according to claim 21, characterized in that when X=Cl, the acid chloride is prepared by reacting the compound wherein X=OH with PCl₃, in chlorinated solvent, and thereafter the obtained acid chloride in situ with R-NH₂.

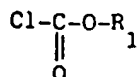
26. A process according to claim 25, characterized in that the
30 chlorinated solvent is selected from the class consisting of

- 18 -

CHCl_3 , CH_2Cl_2 , $\text{Cl}_2\text{-CH-CH-Cl}_2$.

27. A process according to claim 25, characterized in that the preparation of the acid chloride is carried out in the presence of
5 R-NH_2 in excess.

28. A process according to claim 21, characterized in that when X is O-C-O-R_1 , the compound wherein X=OH is reacted in the presence of an aprotic solvent, first with an organic base and thereafter, at a temperature comprised between -10°C and 0°C , with a
10 derivative of the chlorocarbonic acid of the formula



wherein R_1 has the previously specified meaning, the mixed anhydride being then allowed to react with R-NH_2 (wherein R has
15 the meaning specified in claim 1) at a temperature comprised between 10° and 80°C .

29. A process according to claim 28, characterized in that the aprotic solvent is selected from CH_2Cl_2 , dioxane, tetrahydrofurane, diglyme, dimethylsulfoxide and dimethylformamide and the organic
20 base is selected from diisopropylethylamine and dimethylaniline.

30. A process according to claim 28, characterized in that the reaction between the mixed anhydride and R-NH_2 occurs in the same solvent wherein the mixed anhydride has been formed and with 2 molar eq. of the amine.

25 31. Pharmaceutical compositions containing as active ingredient a compound of the general formula (I) together with pharmaceutically acceptable excipients and vehicles.



European Patent
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EUROPEAN SEARCH REPORT

0030009

Application number

EP 80107404.8

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	<u>GB - A - 1 254 771</u> (BP CHEMICALS) + Claims + --	1	C 07 C 103/58 C 07 C 102/04 C 07 D 213/40 C 07 D 213/75
	<u>US - A - 4 024 151</u> (P.C. WADE, B.R. VOGT) + Claims + ----	1	A 61 K 31/225 A 61 K 31/44
			TECHNICAL FIELDS SEARCHED (Int. Cl. 7)
			C 07 C 103/00 C 07 D 213/00 C 07 C 102/00 A 61 K 31/00
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family, corresponding document
<input checked="" type="checkbox"/>	The present search report has been drawn up for all claims		
Place of search VIENNA		Date of completion of the search 16-02-1981	Examiner HOFBAUER